Associations of long-chain ω-3 fatty acids and fish intake with endometrial cancer risk in the VITamins And Lifestyle cohort[1–3]

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ABSTRACT

Background: Inflammation plays an important role in endometrial cancer etiology. Long-chain ω-3 (n−3) polyunsaturated fatty acids (PUFAs), derived from marine sources, are thought to be antiinflammatory; however, several studies of fish consumption suggest an increase in risk.

Objective: This study examined whether intakes of long-chain ω-3 PUFAs, including eicosapentaenoic acid (EPA; 20:5ω-3) and docosahexaenoic acid (DHA; 22:6ω-3), from diet and supplements and intake of fish are associated with endometrial cancer risk.

Design: Between 2000 and 2002, 22,494 women aged 50–76 y, living in western Washington State, were recruited to the VITamins And Lifestyle cohort study. Incident endometrial cancers (n = 263) were identified through the Surveillance, Epidemiology, and End Results cancer registry after 9 y of follow-up. Multivariable-adjusted HRs and 95% CIs for the association of intakes of individual long-chain ω-3 PUFAs and fish with endometrial cancer risk were estimated by using Cox proportional hazards.

Results: Women in the highest compared with the lowest quintile of dietary EPA + DHA intake had a 79% increased risk of endometrial cancer (95% CI: 16%, 175%; P-trend = 0.026). Results were similar for EPA and DHA measured individually and for fish intake. When data were stratified by body mass index (in kg/m^2; $<$25 or $\geq$25), increases in risk of long-chain ω-3 PUFAs were restricted to overweight and obese women, and statistically significant reductions in risk were observed for normal-weight women.

Conclusions: The overall increased risk reported here confirms the findings of several prior observational studies of fish intake, which observed similar increases in risk. Randomized trials are needed to confirm these findings. *Am J Clin Nutr* 2014;99:599–608.

INTRODUCTION

Inflammation plays an important role in the etiology of endometrial cancer (1). Findings from large prospective studies have shown that increases in blood markers of inflammation are associated with increases in endometrial cancer risk (2–4). A recent meta-analysis reported that the use of aspirin is associated with reductions in endometrial cancer risk (5), particularly among obese women. It is estimated that cyclooxygenase 2, a target of aspirin that is responsible for the conversion of arachidonic acid [20:4ω-6 (20:4n−6)] to proinflammatory prostaglandins, is expressed in 35–92% of endometrial cancers (6–8). Intake of long-chain ω-3 PUFAs, such as EPA (20:5ω-3) and DHA (22:6ω-3), which are primarily derived from oily fish and fish-oil supplements, are thought to suppress inflammation through competition with arachidonic acid on cell membranes (9).

Endometrial cancer is the most common gynecologic cancer among women (10), and, although the prognosis from this disease is generally good (10), there is a need to better understand factors that could modify risk. With the exception of obesity (11) and aspirin (12), studies of modifiable lifestyle factors associated with inflammation on endometrial cancer risk are lacking. To date, only one study has examined the association between individual ω-3 PUFAs and endometrial cancer risk (13). Arem et al (13) reported linear reductions in endometrial cancer risk with increasing consumption of long-chain ω-3 fatty acids in a case-control study. Results from several other case-control studies (14–22) and 2 cohort studies (23, 24) that examined dietary fish or seafood intake are mixed.

We examined the associations of dietary and supplemental ω-3 PUFA and fish intakes with endometrial cancer risk among female participants in the large prospective VITamins And Lifestyle (VITAL)[4] cohort study. To our knowledge, this study was the first to prospectively examine intake of specific ω-3 PUFAs in association with endometrial cancer incidence.

SUBJECTS AND METHODS

Study population

Participants in this study were female members of the VITAL cohort—a study of men and women that was designed to prospectively investigate the association between dietary supplement use and cancer risk. Detailed methods are described elsewhere (12, 25). Briefly, men and women aged 50–76 y at baseline who lived in the 13-county region of Western Washington State covered by the Surveillance, Epidemiology and End Results

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[4] Abbreviations used: FFQ, food-frequency questionnaire; SEER, Surveillance, Epidemiology and End Results; VITAL, VITamins And Lifestyle.

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(SEER) cancer registry, were eligible to participate. Because this article is limited to women, we describe here the recruitment of women. Between October 2000 and December 2002, baseline questionnaires and postcard reminders were mailed to 168,953 women by using names from a commercial mailing list. Of these, 40,337 were returned and deemed eligible. We excluded participants with a positive or missing history of uterine (n = 877), ovarian, (n = 22), or breast (n = 1849) cancer at baseline; participants who had a hysterectomy or were missing these data (n = 15,079); and incident diagnoses of in situ endometrial cancer (n = 2) or endometrial cancers of mesenchymal origin or mixed tumor types (n = 14). After the exclusions, there were 22,494 women available for study. All participants gave informed consent, and study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Data collection

Dietary intakes were assessed by using a semiquantitative food-frequency questionnaire (FFQ), adapted from instruments developed for the Women's Health Initiative and other studies (26–28). The measurement properties of earlier versions of this questionnaire have been published (28). Participants reported their usual frequency and portion size (small, medium, or large relative to the stated medium portion size and to photographs of portion sizes) of 120 foods and beverages consumed during the year before baseline. The questionnaire was specifically formulated to improve measurement of fat intake. This was accomplished in part by use of questions to delineate the amount of fats consumed, food preparation, and types of fat added in cooking or at the table. The average daily intake of specific fatty acids was calculated by multiplying the adjusted serving size of each specific food by its fatty acid content. The fatty acid and nutrient compositions of each food were determined by using the University of Minnesota's Nutrient Data System for Research v2006 (29).

Because fish-oil supplements contain high doses of EPA and DHA, we created variables representing dietary plus supplemental exposures to these fatty acids. Participants were asked to report the frequency (d/wk) and duration (y) of fish-oil supplement use in the past 10 y. Data on supplement dose were not available; therefore, we estimated doses of EPA and DHA based on the average suggested daily dose among the most popular brands of fish-oil supplements (640 and 350 mg/d, respectively), which was multiplied by reported days per week/7 and years of use/10 to yield average daily supplemental intakes of EPA and of DHA. Summary variables representing total long-chain ω-3 PUFA exposure were calculated by adding intakes of EPA and DHA from diet and from diet plus supplemental sources; ω-3 from diet and diet plus supplements were categorized into energy-adjusted quintiles by using the residual method (30).

In addition to information on diet and supplement use, information on endometrial cancer risk factors was collected at baseline. Participants reported their demographic and health-related characteristics, including current height and weight [from which BMI (in kg/m^2) was computed], education, family history of cancer, and medical history, including detailed information on reproductive health. Women also answered several questions regarding cigarette smoking behavior, including the number of cigarettes smoked each day and the cumulative years of smoking from which we computed pack-years of smoking.

Follow-up for cancer and censoring

Participants were followed for incident endometrial cancer diagnoses from baseline to 31 December 2010. Incident, primary, invasive endometrial cancers were ascertained by linking the study cohort to the western Washington SEER cancer registry. All incident cancer cases, except nonmelanoma skin cancer, diagnosed within the 13-county region are reported to SEER along with stage, histologic subtype, and other tumor characteristics (31). Cases were ascertained through all area hospitals, offices of pathologists, oncologists, and radiotherapists and from state death certificates. Extensive quality-control procedures ensure that registry data are accurate and complete. After a median follow-up of 9 y, 263 incident, invasive endometrial cancer cases were diagnosed among eligible women.

Participants were right-censored from the analysis at the earliest date of the following events: withdrawal from the study (n = 9), death (n = 1410), emigration out of the SEER catchment region (n = 1478), or 31 December 2010—the most recent date of linkage to the SEER registry (n = 19,334). Deaths that occurred in the cohort were ascertained by linkage to the Washington State death file. The National Change of Address System and active follow-up by telephone calls and mailings were used to identify participants who moved out of the study region.

Statistical analyses

We calculated geometric means of average daily dietary intake of long-chain ω-3 PUFAs (EPA + DHA, mg/d) by categories of participants' baseline characteristics. Age and energy-adjusted ratios and 95% CIs for associations between participants' characteristics and dietary long-chain ω-3 PUFA intakes were estimated in multiple regression models that included log-transformed daily dietary long-chain ω-3 PUFAs as the dependent variable. β-Coefficients and their corresponding 95% CIs are presented as e^{β} and $e^{\beta \pm 1.96(\mathrm{SE})}$, which reflect the ratio and respective CI of ω-3 PUFAs among those in the category of interest relative to the reference category.

Cox proportional hazards regression models using baseline age as the time metric were used to estimate multivariable-adjusted HRs and 95% CIs for the associations between fatty acid or fish intake and endometrial cancer risk. We selected a priori potential confounders for inclusion in multivariable models. Regression models were adjusted for known or suspected risk factors of endometrial cancer, including age (time variable), race, education, BMI, pack-years of smoking, physical activity (metabolic equivalent task-hours/wk), alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of estrogen-only therapy, years of oral contraceptive use, oophorectomy, history of diabetes, total energy intake as a continuous variable, and family histories of uterine, ovarian, and breast cancer (as separate terms) using categories of these variables as given in **Table 1**. P-trend values were calculated by treating ordinal exposure variables as continuous in regression models. The proportionality of hazards was verified by plotting the Schoenfeld residuals against the timeline. All reported P values are 2-sided, and $P < 0.05$ was considered statistically significant.

Because body size is a major risk factor for endometrial cancer, possibly through its effects on estrogen signaling in vivo (32), and

TABLE 1
Association between participants' characteristics and dietary long-chain ω-3 PUFAs in the VITamins And Lifestyle cohort[1]

		EPA + DHA from diet	
Characteristic	*n*	Intake	Age- and energy-adjusted ratio (95% CI)[2]
		mg/d	
Age[3]			
<55 y	6060	109.04 ± 1.02	1.00 (reference)
55–59 y	5095	109.97 ± 1.02	1.02 (0.98, 1.07)
60–65 y	3340	108.16 ± 1.02	1.01 (0.96, 1.07)
65–69 y	2640	110.75 ± 1.03	1.04 (0.98, 1.10)
≥70 y	3100	98.47 ± 1.02	0.95 (0.90, 1.00)
P-trend			0.210
Race			
White	18,842	106.23 ± 1.01	1.00 (reference)
Black	195	130.70 ± 1.08	1.20 (1.01, 1.43)
Other race	1118	130.88 ± 1.04	1.27 (1.18, 1.37)
Education			
≤High school graduate	3995	82.96 ± 1.02	1.00 (reference)
Some college	7804	101.88 ± 1.01	1.22 (1.16, 1.28)
≥College graduate	8347	128.50 ± 1.01	1.51 (1.43, 1.58)
BMI			
<25.0 kg/m^2	8349	109.83 ± 1.02	1.00 (reference)
25.0–29.9 kg/m^2	6308	109.53 ± 1.02	0.97 (0.93, 1.01)
30.0–34.9 kg/m^2	2801	106.11 ± 1.02	0.89 (0.84, 0.94)
≥35.0 kg/m^2	1869	100.33 ± 1.03	0.80 (0.75, 0.85)
P-trend			<0.001
Smoking			
Nonsmoker	11,451	108.08 ± 1.01	1.00 (reference)
<7.5 pack-years	3340	118.58 ± 1.02	1.11 (1.06, 1.17)
7.5–25.0 pack-years	2730	107.62 ± 1.03	1.01 (0.96, 1.07)
≥25.0 pack-years	2612	93.27 ± 1.03	0.85 (0.81, 0.90)
P-trend			<0.001
Alcohol			
Nondrinker	6668	82.25 ± 1.02	1.00 (reference)
<1.0 drink/d	10,132	116.27 ± 1.01	1.31 (1.26, 1.36)
1–1.9 drinks/d	2039	147.23 ± 1.02	1.66 (1.56, 1.77)
≥2.0 drinks/d	1396	141.04 ± 1.03	1.46 (1.36, 1.57)
P-trend			<0.001
Physical activity			
Inactive	2775	81.96 ± 1.02	1.00 (reference)
<3.7 MET-h/wk	5786	98.90 ± 1.02	1.23 (1.17, 1.31)
3.7–11.4 MET-h/wk	5663	111.92 ± 1.02	1.39 (1.32, 1.47)
≥11.4 MET-h/wk	5780	128.73 ± 1.02	1.61 (1.52, 1.70)
P-trend			<0.001
Reproductive health			
Age at menarche			
≤11 y	3453	106.69 ± 1.02	1.00 (reference)
12 y	6040	108.24 ± 1.02	1.03 (0.98, 1.09)
13 y	6100	110.78 ± 1.02	1.06 (1.01, 1.12)
≥14 y	4559	103.24 ± 1.02	0.99 (0.94, 1.05)
P-trend			0.849
Age at menopause			
≤44 y	2358	96.36 ± 1.03	1.00 (reference)
45–49 y	5195	103.78 ± 1.02	1.05 (0.99, 1.12)
≥50 y	10,001	111.38 ± 1.01	1.13 (1.07, 1.20)
Premenopausal	1260	118.72 ± 1.03	1.19 (1.09, 1.30)
Perimenopausal	1014	109.65 ± 1.04	1.08 (0.98, 1.19)
Parity			
Nulliparous	2888	111.67 ± 1.03	1.00 (reference)
1–2	8629	110.64 ± 1.01	1.01 (0.96, 1.06)
3–4	5968	105.39 ± 1.02	0.96 (0.91, 1.02)
≥5	1323	95.80 ± 1.04	0.87 (0.80, 0.94)
P-trend			0.024

(Continued)

TABLE 1 (*Continued*)

Characteristic	EPA + DHA from diet		
	n	Intake	Age- and energy-adjusted ratio (95% CI)[2]
Duration of combined hormone therapy			
Never	9748	104.00 ± 1.01	1.00 (reference)
1–4 y	3285	117.05 ± 1.02	1.12 (1.07, 1.18)
5–9 y	2935	109.23 ± 1.02	1.05 (1.00, 1.11)
≥10 y	3206	110.65 ± 1.02	1.09 (1.03, 1.14)
P-trend			0.670
Duration of estrogen-only hormone therapy			
Never	15,965	108.34 ± 1.01	1.00 (reference)
1–4 y	549	98.61 ± 1.05	0.96 (0.86, 1.06)
5–9 y	852	108.63 ± 1.05	1.02 (0.94, 1.11)
≥10 y	431	105.65 ± 1.03	1.01 (0.90, 1.14)
P-trend			0.795
Duration of oral contraceptive use			
Never	5073	101.55 ± 1.02	1.00 (reference)
≤4 y	7703	110.52 ± 1.01	1.06 (1.01, 1.12)
5–9 y	3755	109.80 ± 1.02	1.08 (1.02, 1.14)
≥10 y	3519	108.26 ± 1.02	1.05 (0.99, 1.11)
P-trend			0.125
Medical and family history			
Oophoerectomy			
No	19,469	107.62 ± 1.01	1.00 (reference)
Yes	766	108.50 ± 1.05	1.01 (0.92, 1.10)
History of diabetes			
No	19,255	108.33 ± 1.01	1.00 (reference)
Yes	980	95.16 ± 1.04	0.87 (0.80, 0.94)
Family history of uterine cancer			
No	18,965	108.03 ± 1.01	1.00 (reference)
Yes	1029	101.52 ± 1.04	0.93 (0.86, 1.01)
Family history of ovarian cancer			
No	19,322	107.52 ± 1.01	1.00 (reference)
Yes	679	112.98 ± 1.04	1.04 (0.94, 1.14)

[1] MET-h, metabolic equivalent task hours.

[2] Regression model predicting the natural logarithm of EPA + DHA. β-Coefficients and corresponding 95% CIs are expressed as e^{β} and $e^{\beta \pm 1.96(SE)}$, reflecting the ratio of EPA to DHA in those in a given category of a characteristic relative to the reference.

[3] Adjusted for energy intake only.

is associated with inflammation (33), we hypothesized that associations would be modified in analyses stratified by BMI (normal weight, <25; overweight or obese, ≥25). *P*-interaction values were calculated by using the likelihood ratio test comparing models with and without a cross-product term between BMI and ω-3 PUFA or fish intake in proportional hazards models. We additionally performed a subgroup analysis restricting associations between diet and endometrial cancer risk to incident endometrial cancers of endometrioid (type I) subtypes (n = 228), which are thought to be estrogen responsive (34). For these analyses, diagnoses of clear cell and serous cell subtypes (n = 35) were right-censored at their respective dates of diagnosis.

RESULTS

The associations between demographic, lifestyle, and reproductive characteristics of women participating in the cohort and endometrial cancer risk are published elsewhere (12). Briefly, women who were older, were obese, had a family history of uterine or ovarian cancer, and had later ages at menopause were at increased risk of endometrial cancer risk, whereas women in the highest compared with lowest categories of smoking, alcohol consumption, physical activity, parity, age at menarche, and duration of oral contraceptive or combined postmenopausal hormone therapy were at reduced risk of endometrial cancer (12).

Associations between participants' characteristics and dietary long-chain ω-3 PUFAs (mg/d), adjusted for age and energy intakes, are shown in Table 1. Nonwhite race, higher levels of education, consumption of alcohol, and physical activity were associated with higher ω-3 PUFA consumption, as was use of combined hormone therapy, being premenopausal, or having a later age at menopause. Compared with women in the lowest category, women in the highest category of age, BMI, smoking, and number of pregnancies and women with a history of diabetes consumed fewer ω-3 PUFAs.

Associations of ω-3 PUFA intakes from diet and diet plus supplements with endometrial cancer risk are given in **Table 2**. Women in the highest quintile of dietary EPA + DHA intake had a 79% higher endometrial cancer incidence (HR: 1.79; 95% CI: 1.16, 2.75), contrasted against the lowest quintile with a linear trend (*P*-trend = 0.026). Associations between the individual

TABLE 2
Association between ω-3 PUFA intake and endometrial cancer risk in the VITamins And Lifestyle cohort[1]

	Energy-adjusted quintiles of fatty acid intake					
	1	2	3	4	5	*P*-trend[2]
ω-3 from diet						
EPA, 20:5ω-3 (mg/d)	≤18	19–35	36–54	55–84	>84	
No. of cases	48	51	45	41	59	
HR (95% CI)[3]	1.00 (reference)	1.25 (0.80, 1.94)	1.13 (0.72, 1.79)	1.16 (0.73, 1.83)	1.73 (1.14, 2.63)	0.027
DHA, 22:6ω-3 (mg/d)	≤40	41–71	72–109	110–171	>171	
No. of cases	48	46	55	40	55	
HR (95% CI)[3]	1.00 (reference)	1.12 (0.71, 1.76)	1.41 (0.91, 2.18)	1.09 (0.69, 1.74)	1.66 (1.09, 2.55)	0.036
EPA + DHA (mg/d)	≤60	61–106	107–164	165–256	>256	
No. of cases	45	53	47	43	56	
HR (95% CI)[3]	1.00 (reference)	1.37 (0.88, 2.15)	1.25 (0.79, 1.98)	1.25 (0.79, 1.99)	1.79 (1.16, 2.75)	0.026
ALA, 18:3ω-3 (mg/d)	≤883	884–1088	1089–1300	1301–1615	>1615	
No. of cases	56	45	45	52	46	
HR (95% CI)[3]	1.00 (reference)	0.83 (0.55, 1.27)	0.79 (0.51, 1.23)	0.96 (0.63, 1.44)	0.85 (0.56, 1.29)	0.687
ω-3:ω-6						
Ratio of EPA + DHA to LA + AA (mg/d)	0.0052	0.0053–0.0105	0.0106–0.0170	0.0171–0.0277	>0.0277	
No. of cases	45	48	57	40	54	
HR (95% CI)[3]	1.00 (reference)	1.05 (0.67, 1.65)	1.29 (0.82, 2.01)	1.01 (0.63, 1.61)	1.61 (1.04, 2.50)	0.061
ω-3 from diet plus supplement						
EPA, 20:5ω-3 (mg/d)	≤20	21–38	39–60	61–105	>105	
No. of cases	52	53	46	46	47	
HR (95% CI)[3]	1.00 (reference)	1.19 (0.78, 1.81)	1.05 (0.67, 1.64)	1.16 (0.75, 1.80)	1.23 (0.80, 1.89)	0.418
DHA, 22:6ω-3 (mg/d)	≤43	44–75	76–118	119–191	>191	
No. of cases	54	45	55	38	52	
HR (95% CI)[3]	1.00 (reference)	0.98 (0.63, 1.52)	1.21 (0.79, 1.84)	0.93 (0.59, 1.46)	1.35 (0.89, 2.06)	0.229
EPA + DHA (mg/d)	≤65	66–115	116–181	182–298	>299	
No. of cases	53	49	46	44	52	
HR (95% CI)[3]	1.00 (reference)	1.06 (0.69, 1.63)	1.01 (0.65, 1.57)	1.08 (0.70, 1.67)	1.33 (0.88, 2.01)	0.211

[1] AA, arachidonic acid; ALA, α-linolenic acid; LA, linoleic acid.
[2] Calculated by treating ordinal exposure variables as continuous in regression models.
[3] Derived from Cox proportional hazards regression models. Adjusted for age (time variable), race, education, BMI, pack-years of smoking, physical activity, alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of estrogen-only therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, and total energy.

fatty acids EPA and DHA and endometrial cancer risk were similar to the aggregate measure. No association was found between α-linolenic acid, which does not come from marine sources, and endometrial cancer risk. The ratio of dietary EPA + DHA to ω-6 PUFAs, arachidonic acid + linoleic acid (8:2ω-6) was no more informative than EPA + DHA alone in a comparison of quintile 5 with quintile 1 (HR: 1.61; 95% CI: 1.04, 2.50). When supplemental exposures were examined in conjunction with dietary intakes, associations for EPA, DHA, and EPA + DHA, although elevated, were not statistically significant. When cancers were restricted to endometrioid subtypes, associations with ω-3 PUFA were unchanged (data not shown).

Associations between fish consumption and endometrial cancer risk are given in **Table 3**. Total fish consumption and consumption of baked or broiled fish were associated with linear increases in endometrial cancer risk. Relative to nonconsumers, women who consumed the highest category of total fish had a >2-fold increased risk of endometrial cancer (HR: 2.28; 95% CI: 1.07, 4.87). The findings for baked or broiled fish were driven equally by consumption of canned tuna or tuna casserole, white fish, and dark or oily fish, although findings for each individually were statistically nonsignificant and nonlinear. Consumption of fried fish or shellfish was not associated with endometrial cancer risk.

We further examined whether associations between ω-3 PUFA or fish intake and endometrial cancer risk were modified by body size. For associations of intake of EPA and DHA (separately and combined and from diet alone and diet plus supplements) with endometrial cancer risk, a significant interaction was observed by BMI (all *P*-interactions ≤ 0.004) (**Table 4**). Increasing consumption of EPA, DHA, and EPA + DHA was associated with reduced risks of endometrial cancer among normal-weight women and linear increased risks among women who were overweight or obese. For women with a BMI < 25, those who consumed the highest amounts of EPA + DHA from diet had a 61% lower risk of endometrial cancer (HR: 0.39; 95% CI: 0.16, 0.97; *P*-trend = 0.046). For women with a BMI ≥ 25, those who consumed the highest amounts of EPA + DHA from diet had a nearly 3-fold higher risk of endometrial cancer (HR: 2.75; 95% CI: 1.62, 4.68; *P*-trend < 0.001). When supplemental exposures were considered in addition to diet, the findings were similar (Table 4). We additionally restricted cancers to endometrioid subtypes in analyses stratified on BMI (*see* Supplemental Table 1 under "Supplemental data" in the online issue). Associations for EPA, DHA, and EPA + DHA from diet and diet plus supplements were similar to the analysis including all cases. Significant linear trends were observed for women in both strata, and *P*-interaction values remained statistically significant.

TABLE 3
Association between fish consumption and endometrial cancer risk in the VITamins And Lifestyle cohort

	Categories of serving size–adjusted servings/wk					*P*-trend[1]
Total fish (servings/wk)	0	0.01–1.00	1.01–2.10	2.11–3.08	≥3.09	
No. of cases	11	68	74	37	54	
HR (95% CI)[2]	1.00 (reference)	1.46 (0.70, 3.06)	1.36 (0.65, 2.83)	1.54 (0.70, 3.37)	2.28 (1.07, 4.87)	0.010
Baked or broiled fish (servings/wk)	0	0.01–0.70	0.71–1.48	1.49–2.24	≥2.25	
No. of cases	20	72	64	28	60	
HR (95% CI)[2]	1.00 (reference)	0.99 (0.57, 1.72)	0.91 (0.52, 1.59)	0.86 (0.46, 1.62)	1.72 (0.97, 3.04)	0.015
Canned tuna/tuna casserole (servings/wk)	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
No. of cases	48	57	18	61	60	
HR (95% CI)[2]	1.00 (reference)	1.07 (0.71, 1.63)	1.11 (0.63, 1.95)	1.24 (0.83, 1.86)	1.26 (0.83, 1.91)	0.195
White fish (servings/wk)	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
No. of cases	80	57	13	46	48	
HR (95% CI)[2]	1.00 (reference)	0.91 (0.63, 1.32)	0.84 (0.45, 1.60)	1.13 (0.77, 1.67)	1.33 (0.91, 1.95)	0.109
Dark or oily fish (servings/wk)	0	0.01–0.21	0.22–0.56	0.57–0.77	≥0.78	
No. of cases	84	60	52	7	41	
HR (95% CI)[2]	1.00 (reference)	1.19 (0.83, 1.71)	1.12 (0.77, 1.63)	1.36 (0.62, 3.00)	1.44 (0.96, 2.17)	0.093
Shellfish, not fried (servings/wk)	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
No. of cases	118	50	13	35	28	
HR (95% CI)[2]	1.00 (reference)	1.00 (0.70, 1.42)	1.14 (0.62, 2.08)	1.36 (0.91, 2.03)	1.36 (0.86, 2.15)	0.069
Fried fish or shellfish (servings/wk)	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
No. of cases	134	56	7	29	18	
HR (95% CI)[2]	1.00 (reference)	1.30 (0.94, 1.81)	0.86 (0.40, 1.85)	1.22 (0.80, 1.87)	0.89 (0.53, 1.51)	0.890

[1] Calculated by treating ordinal exposure variables as continuous in regression models.
[2] Derived from Cox proportional hazards regression models. Adjusted for age (time variable), race, education, BMI, pack-years of smoking, physical activity, alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of estrogen-only therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, and total energy.

Similar to findings for ω-3 PUFAs, the associations of total fish, baked or broiled fish, and dark or oily fish with endometrial cancer were modified by BMI (*P*-interactions < 0.02) (**Table 5**). However, point estimates and *P*-trend values were statistically significant only among overweight or obese women.

DISCUSSION

In this large prospective study of women, consumption of long-chain ω-3 PUFAs or their fish sources was associated with increases in endometrial cancer risk overall; however, findings were disparate based on women's body mass, and their consumption was associated with increases in risk among overweight and obese women and decreases in risk among normal-weight women.

Our findings of increased endometrial cancer risk with long-chain ω-3 intake differ from those reported by Arem et al (13) in a population-based case-control study of women in Connecticut. In that study, comparisons of the highest quartile of EPA (OR: 0.57; 95% CI: 0.39, 0.84) and DHA (OR: 0.64; 95% CI: 0.44, 0.94) with the lowest were associated with linear reductions in endometrial cancer risk. Inclusion of supplemental ω-3 PUFAs had a minimal effect on point-estimates. The study by Arem et al is, to our knowledge, the only prior published study to have examined specific ω-3 PUFAs from the diet in relation to endometrial cancer risk. It is unclear why their findings differ from our own. Case-control studies of diet and cancer are susceptible to forms of bias that prospective studies are not (35). The controls in the study were more active, were lighter, were more likely to use fish-oil supplements, and were more educated than the cases. If controls were, on average, more likely to eat fish (a healthy behavior), it is possible that a spurious inverse association would have been observed (13).

Other studies, including several case-control studies (14–22) and 2 prospective cohort studies (23, 24), have examined associations between fish intake and endometrial cancer risk. Notably, findings from the Iowa Women's Health Study cohort (23) and from 2 case-control analyses from the same study conducted 7 y apart (15, 17) in Shanghai, China, support an increased risk. In the Iowa Women's Health Study, a prospective study that included 216 endometrial cancer cases, the highest compared with the lowest tertile of seafood consumption was associated with a 40% increased risk of endometrial cancer (RR: 1.4; CI not given) and a 2-fold risk of endometrial cancer for cases diagnosed ≥5 y after baseline (RR: 2.0; *P*-trend < 0.05). In the most recent of the 2 case-control analyses among Chinese women, Xu et al (17) found that fish consumption was positively and linearly associated with endometrial cancer risk in a comparison of quintile 4 with quintile 1 (OR: 2.4; 95% CI: 1.8, 3.1; *P*-trend < 0.01). Point estimates for specific fish types (marine, fresh water, shellfish, etc) were also elevated and statistically significant. A 2013 analysis of the NIH-AARP Diet and Health cohort (no. of cases = 1486) reported that total fish intake was associated with a statistically nonsignificant 10% increased endometrial cancer risk in a comparison of quintile 5 with quintile 1 (HR: 1.10; 95% CI: 0.93, 1.29) (24). Specific types of fish (white fish compared with fatty fish) were not examined (24). Several other case-control studies reported either a reduction in risk (14, 16) or no association (18–22). A 2007 meta-analysis of case-control studies reported no association between fish intake with endometrial cancer risk (OR: 1.04; 95% CI: 0.55, 1.98) (36) among 7 studies; however, when the analysis was restricted to 4 studies deemed by the authors as "higher quality" (criteria included adjustment for energy and BMI, exclusion of hysterectomies from control groups, and ≥200 cases), the findings

TABLE 4
Association between long-chain ω-3 PUFAs and endometrial cancer risk, stratified by BMI

	Energy-adjusted quintiles of fatty acid intake					
	1	2	3	4	5	*P*-trend[1]
ω-3 from diet						
EPA, 20:5ω-3 (mg/d)	≤18	19–35	36–54	55–84	>84	
BMI <25 kg/m^2	1.00 (reference)[2]	0.71 (0.32, 1.54)	0.57 (0.25, 1.28)	0.60 (0.27, 1.31)	0.42 (0.18, 0.99)	0.052
BMI ≥25 kg/m^2	1.00 (reference)	1.53 (0.88, 2.68)	1.46 (0.82, 2.60)	1.49 (0.83, 2.66)	2.62 (1.55, 4.41)	<0.001
P-interaction[3]						0.004
DHA, 22:6ω-3 (mg/d)	≤40	41–71	72–109	110–171	>171	
BMI <25 kg/m^2	1.00 (reference)	0.62 (0.27, 1.44)	0.90 (0.43, 1.90)	0.53 (0.23, 1.20)	0.35 (0.14, 0.85)	0.023
BMI ≥25 kg/m^2	1.00 (reference)	1.43 (0.81, 2.52)	1.54 (0.88, 2.71)	1.52 (0.85, 2.72)	2.60 (1.53, 4.40)	<0.001
P-interaction[3]						0.002
EPA + DHA (mg/d)	≤60	61–106	107–164	165–256	>256	
BMI <25 kg/m^2	1.00 (reference)	0.87 (0.39, 1.94)	0.69 (0.30, 1.55)	0.72 (0.33, 1.58)	0.39 (0.16, 0.97)	0.046
BMI ≥25 kg/m^2	1.00 (reference)	1.71 (0.98, 3.00)	1.48 (0.82, 2.65)	1.60 (0.89, 2.89)	2.75 (1.62, 4.68)	<0.001
P-interaction[3]						0.004
ω-3 from diet plus supplement						
EPA, 20:5ω-3 (mg/d)	≤20	21–38	39–60	61–105	>105	
BMI <25 kg/m^2	1.00 (reference)	0.64 (0.30, 1.37)	0.45 (0.20, 1.02)	0.66 (0.32, 1.35)	0.19 (0.07, 0.54)	<0.001
BMI ≥25 kg/m^2	1.00 (reference)	1.50 (0.88, 2.57)	1.43 (0.82, 2.50)	1.34 (0.75, 2.38)	2.11 (1.26, 3.55)	0.016
P-interaction[3]						0.002
DHA, 22:6ω-3 (mg/d)	≤43	44–75	76–118	119–191	>191	
BMI <25 kg/m^2	1.00 (reference)	0.47 (0.20, 1.10)	0.82 (0.40, 1.65)	0.38 (0.16, 0.88)	0.28 (0.12, 0.68)	0.005
BMI ≥25 kg/m^2	1.00 (reference)	1.29 (0.75, 2.23)	1.28 (0.73, 2.22)	1.36 (0.78, 2.37)	2.09 (1.25, 3.50)	0.009
P-interaction[3]						0.002
EPA + DHA (mg/d)	≤65	66–115	116–181	182–298	>299	
BMI <25 kg/m^2	1.00 (reference)	0.57 (0.26, 1.25)	0.55 (0.26, 1.20)	0.57 (0.27, 1.21)	0.29 (0.12, 0.70)	0.012
BMI ≥25 kg/m^2	1.00 (reference)	1.38 (0.80, 2.36)	1.18 (0.67, 2.07)	1.44 (0.83, 2.50)	2.04 (1.22, 3.42)	0.011
P-interaction[3]						0.004

[1] Calculated by treating ordinal exposure variables as continuous in regression models. Adjusted for age (time variable), race, education, BMI, pack-years of smoking, physical activity, alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of estrogen-only therapy, years of oral contraceptive use, oophoerectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, and total energy.

[2] HR; 95% CI in parentheses (all such values). Values are derived from Cox proportional hazards regression models.

[3] Calculated by using the likelihood ratio test.

were remarkably similar to our own (OR: 1.88; 95% CI: 1.20, 2.95). Note that we found that the consumption of all types of fish, except for fried fish and shellfish, were associated with an increased risk of endometrial cancer. The ω-3 content varies substantially across different types of fish, and this finding therefore opens up the possibility that some other component of fish, other than ω-3 content, could be responsible for the observed increased risk.

Only the NIH-AARP study examined the interaction of total fish intake with BMI. The findings were statistically nonsignificant ($P > 0.1$) (24). We know of no prior study that has examined associations between long-chain ω-3 PUFAs or fish types and endometrial cancer risk stratified by BMI. Given the strength of our findings and the observed interactions, replication in other studies is warranted.

Long-chain ω-3 PUFAs have several physiologic effects. Because of their suppressive effects on inflammation pathways, including inhibition of tumor necrosis factor α and modification of prostaglandin synthesis, they are considered antiinflammatory (37). ω-3 PUFAs have other properties, however, that are less well understood with regard to tumorigenesis: they are prooxidative in high doses (38) and affect cell permeability, motility, and signal transduction (37). Perhaps most importantly, long-chain ω-3 fatty acids may increase in vivo sex hormone concentrations, which are major drivers of endometrial proliferation (39, 40). In a randomized, double-blind trial of 90 women assigned to fish oil (2.2 g) or a placebo for 12 wk, the intervention increased serum estradiol ($P = 0.02$) and estrone ($P = 0.04$) among pre- but not postmenopausal women (41). In a smaller controlled, crossover feeding trial of 16 postmenopausal women, a low-fat diet and a low-fat, high ω-3 diet were associated with a higher excretion of urinary estrogens (42). In the same study, no relative increase in sex hormones measured in blood was found (43). It is possible that, in overweight and obese women, increased estrogen production from adipose tissue in conjunction with that from ω-3 intake may lead to a greater risk. Some have hypothesized that an increase in risk could be explained by contamination of fish with persistent environmental pollutants (36); however, evidence that organochlorines cause mutagenesis in experimental studies of cells (44) and animals (45) is limited, and epidemiologic studies have not shown an association (46, 47).

This study had several strengths, including its prospective design, large sample size, and near-complete follow-up of participants. In addition, the FFQ was designed specifically to improve the measurement of fat intake. We were additionally able to assess dietary supplement exposures, which is different from most studies. Another major strength was our ability to

TABLE 5
Association between fish consumption and endometrial cancer risk, stratified by BMI

	Categories of serving size–adjusted servings/wk					*P*-trend[1]
Total fish (servings/wk)	0	0.01–1.00	1.01–2.10	2.11–3.08	≥3.09	
BMI						
<25 kg/m^2	1.00 (reference)[2]	0.63 (0.24, 1.73)	0.51 (0.19, 1.39)	0.59 (0.19, 1.77)	0.39 (0.12, 1.26)	0.191
≥25 kg/m^2	1.00 (reference)	2.30 (0.71, 7.47)	2.42 (0.75, 7.81)	2.40 (0.71, 8.17)	5.04 (1.54, 16.50)	<0.001
P-interaction						0.017
Baked or broiled fish (servings/wk)	0	0.01–0.70	0.71–1.48	1.49–2.24	≥2.25	
BMI						
<25 kg/m^2	1.00 (reference)	0.54 (0.23, 1.27)	0.38 (0.16, 0.91)	0.36 (0.13, 0.99)	0.43 (0.16, 1.13)	0.124
≥25 kg/m^2	1.00 (reference)	1.35 (0.60, 3.03)	1.45 (0.65, 3.26)	1.40 (0.58, 3.38)	2.87 (1.27, 6.51)	<0.001
P-interaction[3]						0.015
Canned tuna/tuna casserole (servings/wk)	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
BMI						
<25 kg/m^2	1.00 (reference)	0.92 (0.45, 1.87)	0.48 (0.14, 1.68)	0.77 (0.36, 1.65)	1.03 (0.49, 2.17)	0.831
≥25 kg/m^2	1.00 (reference)	1.24 (0.71, 2.17)	1.37 (0.66, 2.85)	1.78 (1.06, 3.01)	1.57 (0.91, 2.69)	0.038
P-interaction						0.299
White fish (servings/wk)[4]	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
BMI						
<25 kg/m^2	1.00 (reference)	0.85 (0.44, 1.66)	0.54 (0.16, 1.83)	0.67 (0.31, 1.43)	0.64 (0.29, 1.42)	0.185
≥25 kg/m^2	1.00 (reference)	0.84 (0.52, 1.33)	0.86 (0.38, 1.91)	1.20 (0.75, 1.93)	1.65 (1.05, 2.58)	0.019
P-interaction						0.059
Dark or oily fish (servings/wk)[4]	0	0.01–0.21	0.22–0.56	0.57–0.77	≥0.78	
BMI						
<25 kg/m^2	1.00 (reference)	1.52 (0.79, 2.93)	0.73 (0.34, 1.54)	0.72 (0.09, 5.57)	0.48 (0.19, 1.20)	0.033
≥25 kg/m^2	1.00 (reference)	0.93 (0.59, 1.48)	1.23 (0.79, 1.92)	1.63 (0.68, 3.88)	1.69 (1.05, 2.73)	0.017
P-interaction						0.012
Shellfish, not fried (servings/wk)[4]	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
BMI						
<25 kg/m^2	1.00 (reference)	0.91 (0.48, 1.75)	1.70 (0.65, 4.48)	0.76 (0.31, 1.87)	1.14 (0.46, 2.83)	0.958
≥25 kg/m^2	1.00 (reference)	1.04 (0.67, 1.61)	0.92 (0.40, 2.13)	1.70 (1.08, 2.69)	1.56 (0.90, 2.70)	0.020
P-interaction						0.406
Fried fish or shellfish (servings/wk)[4]	0	0.01–0.21	0.22–0.35	0.36–0.56	≥0.57	
BMI						
<25 kg/m^2	1.00 (reference)	1.35 (0.71, 2.58)	1.84 (0.56, 6.08)	1.11 (0.43, 2.87)	0.70 (0.21, 2.34)	0.960
≥25 kg/m^2	1.00 (reference)	1.39 (0.93, 2.07)	0.52 (0.16, 1.65)	1.31 (0.80, 2.14)	1.14 (0.63, 2.06)	0.501
P-interaction						0.671

[1] Calculated by treating ordinal exposure variables as continuous in regression models.
[2] HR; 95% CI in parentheses (all such values). Values are derived from Cox proportional hazards regression models.
[3] Calculated by using the likelihood ratio test.
[4] Adjusted for age (time variable), race, education, BMI, pack-years of smoking, physical activity, alcohol consumption, age at menarche, age at first birth, age at menopause, parity, years of combined hormone therapy, years of estrogen-only therapy, years of oral contraceptive use, oophorectomy, family history of uterine cancer, family history of ovarian cancer, history of diabetes, and total energy.

statistically control for many potential confounders, although BMI was self-reported rather than measured. This study was not without its limitations. FFQ-derived nutrient data can be unreliable (35); however, we expect the measurement error to be nondifferential by disease status, so the observed associations would be attenuated toward the null. It is also possible that we were unable to fully control for energy intake in regression models because of underestimation of intake (28, 48). Although some of the increase in risk observed could be explained by residual confounding, it does not explain the strong associations in opposite directions that we observed in the analyses stratified by BMI.

Increased intake of long-chain ω-3 PUFAs has been widely promoted for the prevention and treatment of several chronic diseases, despite recent evidence indicating that some public health recommendations may have been premature (49). In this large prospective study, we found that intake of long-chain ω-3 PUFAs and their food sources are positively associated with endometrial cancer risk among overweight and obese women. In normal-weight women, long-chain ω-3 fatty acids may provide some benefit. The overall association that we report here is not novel, because several prior studies of fish intake have observed similar increases in risk overall. Their replication here, however, adds support for these findings and lends strong motivation for further study. Because this is an observational study, replication in randomized trials is necessary to confirm these findings. One such study, the ongoing VITamin D and Omega-3 TriAL (VITAL) (50), may be helpful in verifying the results we report here.

The authors' responsibilities were as follows—TMB: designed the research, analyzed the data, and wrote the manuscript; EW: designed and conducted the research and had primary responsibility for the final content; and MLN and DEC: wrote the manuscript and assisted in the research design and analysis plan. All authors contributed to the analyses and read and approved the final manuscript. The sponsors had no role in the study's design, data collection, analyses, or interpretation of results; the preparation of

the manuscript; or the decision to submit the manuscript for publication. None of the authors had a conflict of interest to declare.

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